

FDA/CDC/NLM Workshop on Promoting Semantic Interoperability of Laboratory Data

*The information and questions contained in this document are not binding and do not create new requirements or expectations for affected parties, nor is this document meant to convey FDA's recommended approaches or guidance. Rather the information contained in this document offers background and the basis for discussions at the Public Workshop.*

## **A. Background**

The Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), the National Library of Medicine (NLM) of the National Institutes of Health (NIH), and other entities from government, industry, and academia have long recognized the essential role of semantic interoperability of laboratory test results in health care information technology. For the purposes of this discussion paper and workshop, we have adopted the same definition of interoperability laid out by Office of the National Coordinator for Health IT (ONC) in its (draft) Shared Nationwide Interoperability Roadmap. Specifically, interoperability is intended to mean: the ability of a system to exchange electronic health information with and use electronic health information from other systems without special effort on the part of the user, and for semantic interoperability, the ability of this data to be shared with unambiguous meaning. Many successful efforts have thus far made substantial contributions to different aspects of semantic interoperability, with LOINC® (Logical Observation Identifiers Names and Codes), SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms), and UCUM (Unified Code for Units of Measure) perhaps most recognizable. The influence of these standards has led to the adoption of LOINC and SNOMED-CT as part of health IT certification criteria adopted by ONC.<sup>1</sup> ONC, and others, have highlighted the importance of enabling laboratory interoperability for realizing the vision of an integrated medical care system that provides optimal care in the 21<sup>st</sup> century. In the setting of increased systems-based health care, it is increasingly important for laboratory devices and systems to have the capability to efficiently and unambiguously communicate with other systems, regardless of their location or setting (e.g., hospital-based laboratories, reference laboratories, physician office laboratories, home use testing, etc.).

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<sup>1</sup> <http://www.healthit.gov/policy-researchers-implementers/meaningful-use-regulations>

Laboratories in the 21<sup>st</sup> century serve far more stakeholders than traditional models, with different stakeholders having individual needs and varying use cases.

As federal agencies involved in different aspects of interoperability, FDA, CDC, and NLM have long communicated on how to address various issues of interoperability. Semantic interoperability has been of particular focus for each of these agencies. The short-term and long-term benefits of semantic interoperability have been promoted by a wide range of stakeholders<sup>2</sup> and include enhanced portability of medical records, improved medical decision support, the ability to track public health emergencies, and serving as an enabler of new and more efficient medical research.<sup>3</sup> In a collaborative effort, each agency aims to utilize its unique role and position to contribute to efforts to promote and enhance semantic interoperability.

The intent of this discussion paper and the upcoming September 28, 2015 Public Workshop, *Promoting Semantic Interoperability of Laboratory Data*, are to solicit discussion and feedback regarding potential means by which FDA, NLM, and CDC can promote and enhance the semantic interoperability of laboratory data.

**This discussion paper is intended solely for the purpose of promoting discussion at the upcoming September 28, 2015 workshop.**

The discussion items below, which will serve as a framework for the workshop, are areas where FDA, CDC, and NLM believe that cooperative, concrete steps can benefit the public health without adding burden to stakeholders, e.g., without disrupting established laboratory workflow or adding significant new obligations to industry. Due to advancements in medical technologies there are many evolving areas, e.g., high throughput genomic sequencing or synoptic pathology reports<sup>4</sup>, where interoperability standards are evolving rapidly and would be better addressed in future interactions; the discussion at the workshop will be primarily focused on the discussion items below that are most likely to represent achievable goals, i.e.,

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<sup>2</sup> <http://www.healthit.gov/policy-researchers-implementers/interoperability>

<sup>3</sup> Drawz PE, Archdeacon P, McDonald CJ, Powe NR, Smith KA, Norton J, Williams DE, Patel UD, Narva A. CKD as a Model for Improving Chronic Disease Care through Electronic Health Records. Clin J Am Soc Nephrol. 2015 Jun 25. pii: CJN.00940115. [Epub ahead of print] PMID: 26111857

<sup>4</sup> [http://www.cap.org/apps/docs/committees/cancer/cancer\\_protocols/synoptic\\_report\\_definition\\_and\\_examples.pdf](http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/synoptic_report_definition_and_examples.pdf)

the current ‘low hanging fruit’ that may have substantial clinical impact over a shorter period of time. These areas have been selected as being relatively mature efforts where steps at coordination could substantially enhance interoperability.

One goal of the public workshop is to discuss the utility of promoting greater adoption of interoperable codes and terminologies, facilitating the model that each *in vitro* diagnostic (IVD) device would be associated with a set of predefined LOINC codes that identified the distinct observations produced by the device, that observations with numeric values would be associated with the UCUM representation of their reporting units and that observations with categorical (multiple choice) values would be associated with a SNOMED response set that defined the possible values. Another workshop goal is to discuss the alternative methods for distributing the standard codes associated with a measure (or defined UCUM representation) with a single access mechanism (e.g., by Structured Product Label (SPL)), or by a centralized database resource), or other mechanisms could have an immediate impact on laboratory interoperability. The addition of Unique Device Identifier (UDI) codes<sup>5</sup> has the potential to complete the interoperable description of an *in vitro* laboratory test by identifying the specific device responsible for performing the test to the other codes mentioned above.

## **B. LOINC (Logical Observation Identifiers Names and Codes)**

LOINC<sup>6</sup>, maintained by Regenstrief Institute (Regenstrief), is the lingua franca of laboratory testing, best described as ‘a universal code system that facilitates exchange, pooling, and processing of clinical data.’ LOINC is freely available for commercial and non-commercial uses and is an important component of meaningful use as a primary vocabulary standard.<sup>7,8</sup> It is also included in the NLM Value Set Authority Center, and is a 514(c) recognized standard by

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<sup>5</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/>

<sup>6</sup> <https://loinc.org/>

<sup>7</sup> Health IT Standards Committee. Recommendations to ONC on the assignment of code sets to clinical concepts [data elements] for use in quality measures. [Letter] [Internet]. 2011; Available from: [http://healthit.hhs.gov/portal/server.pt/gateway/PTARGS\\_0\\_12811\\_955546\\_0\\_0\\_18/HITSC\\_CQMWG\\_VTF\\_Transmit\\_090911.pdf](http://healthit.hhs.gov/portal/server.pt/gateway/PTARGS_0_12811_955546_0_0_18/HITSC_CQMWG_VTF_Transmit_090911.pdf)

<sup>8</sup> Office of the National Coordinator for Health Information Technology (ONC) Department of Health and Human Services (HHS). Health Information Technology: Standards, Implementation Specifications, and Certification Criteria for Electronic Health Record Technology, 2014 Edition; Revisions to the Permanent Certification Program for Health Information Technology, 77(171) Fed. Reg. 2012

FDA/CDRH,<sup>9</sup> and CDC.<sup>10</sup> LOINC is used widely internationally: it includes translations into multiple languages<sup>11</sup> and is the official standard for laboratory tests for numerous nations.<sup>12</sup>

Despite widespread use of LOINC, challenges with adoption and implementation remain. The technical, administrative, and financial burden to laboratories of assigning LOINC codes to the specific *in vitro* tests they perform may be significant despite publicly available user-friendly tools to aid LOINC adoption. The granularity of LOINC coding can lead to inconsistency through different coding choices across laboratories for the same test, e.g., one laboratory may choose a code with a specified type of method and the other a more general code that specifies no particular method. In other circumstances an incorrect code may be selected due to a failure to recognize important but subtle distinctions between two similar codes. Laboratory software systems may also vary in their coding practices, leading to further inconsistency.

IVD manufacturers/developers represent the best resource for understanding the unique aspects of the tests they market and are likely best positioned to either identify the correct LOINC code or to specify the information in a request for a new LOINC code. A number of IVD manufacturers already request codes for their new IVD tests from the Regenstrief Institute (the developer of LOINC) and/or have verified their LOINC mappings to existing tests with Regenstrief and now deliver these mappings to the customers through various mechanisms.

Recognizing, however, that this may reflect an unfamiliar process for IVD manufacturers/developers, one area for discussion at the workshop will be how FDA's interaction with the device industry and public health agencies can be leveraged to promote a voluntary approach to adoption. The identification of LOINC codes for new IVDs could then be addressed by industry during device development and 'confirmed' via the pre-submission, the device review process, or other mechanisms. These codes could subsequently be referred to directly or indirectly in device labeling and serve as one source of a 'master index' following

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<sup>9</sup> <https://www.federalregister.gov/articles/2015/01/27/2015-01420/food-and-drug-administration-modernization-act-of-1997-modifications-to-the-list-of-recognized>

<sup>10</sup> <http://phinvads.cdc.gov/vads/ViewValueSet.action?oid=2.16.840.1.114222.4.11.1002>

<sup>11</sup> <https://loinc.org/international>

<sup>12</sup> Logical Observation Identifiers Names and Codes (LOINC® Users' Guide (June 2015), available at <https://loinc.org/downloads/files/LOINCManual.pdf>

laboratory adoption of these devices.. There is precedent for reference to LOINC codes in device labeling: FDA has permitted several devices to be cleared with labeling that referred to specific LOINC codes for the device or reference to a manufacturer-supported web site where LOINC codes were available.<sup>13</sup>

There are well-defined benefits to proposals for a mechanism to provide unambiguous device-associated LOINC codes. Device manufacturers could benefit by more seamless adoption of devices, it could enhance the availability of expertise for identifying appropriate codes, and laboratories could be freed from the burden of individually assigning LOINC codes for each device. Adoption by software/LIS vendors could address the interoperability across systems, and public health authorities could immediately benefit by the ability to aggregate and track anonymized results, particularly in the setting of public health emergencies where rapid adoption of new IVDs and technologies is essential.

However, although benefits are readily apparent, equally so are the challenges inherent in these proposals:

- If FDA were to adopt an important role in this process, FDA or any similar third party efforts to promote standardization may need to be voluntary and necessitate a strong commitment by IVD manufacturers.
- If FDA were to adopt an important role in this process, there may need to be consideration of means to support coding for manufacturers of IVD devices not subject to FDA premarket review, as well as mechanisms to address possible off-label device use.
- If FDA were to adopt an important role in this process, increased FDA LOINC expertise/training would be necessary, and a mechanism for confidential consultation between Regenstrief and FDA may be essential when new LOINC codes are needed.

The ultimate goal would be the opportunity to potentially improve consistency of LOINC code mapping across manufacturers and devices, and enable a process whereby 'authoritative' LOINC codes would be available at the time of device marketing. However, regardless of

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<sup>13</sup> See pages 16-17 at [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K111507.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K111507.pdf).

whether FDA, Regenstrief, or another organization were to serve a role as a knowledgeable authority for assistance in assigning LOINC codes to diagnostic devices, a mechanism to facilitate the assigning of codes by manufacturers/sponsors may be necessary.

Given these considerations, we anticipate the LOINC panelists addressing the following general questions:

- Most of the panel has had direct experience with LOINC; from your experience, what are the general technical and pragmatic challenges (if they exist) to assigning LOINC codes to IVD tests?
- What are some potential mechanisms for the facilitation of assigning LOINC codes as a means to insure consistency across new IVDs? What are the challenges for currently marketed *in vitro* diagnostic devices that should be addressed, and how can FDA, NLM, CDC, and other agencies such as ONC or CMS contribute to this process?
- What are other possible means that the Regenstrief Institute and agencies such as FDA, CDC, NLM, and ONC can support and facilitate laboratory adoption of consistent LOINC coding?
- What are ways to facilitate manufacturer/distributor adoption of LOINC coding to be associated with *in vitro* diagnostic devices?
- How could existing implementations/applications of LOINC be leveraged for interoperability?

### C. SNOMED CT (Systematized Nomenclature of Medicine – Clinical Terms)

SNOMED CT<sup>14</sup> is a systematic set of codes, terms, and definitions maintained by the International Health Terminology Standards Development Organisation (IHTSDO) to describe applicable areas of diseases, findings, procedures, infectious disease agents, etc., for clinical medicine. The use of SNOMED concept IDs to describe qualitative IVD results has been implemented in numerous systems, often with associated LOINC coding of laboratory tests, i.e., 'LOINC identifies the question and SNOMED identifies the answer.' In the context of IVDs,

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<sup>14</sup> <http://www.ihtsdo.org/snomed-ct>

SNOMED CT codes would be used as standardized descriptors for test “answers” rather than as an organized hierarchy. At present, LOINC creates answer lists for each submitted laboratory test with answers that correspond exactly to the answer text provided by the instrument or test kits submitter. LOINC creates its answer codes as “LA codes” for each answer, and provides a slot intended for a corresponding SNOMED, but has only obtained and distributed such codes for a small number of LOINC terms at this point in time.

One approach to conceptualizing the use of LOINC and SNOMED for interoperability may be separating less complicated examples of reporting versus cases with alternative conceptualizations or alternatives that may require recommendations for use. For example, specific tests for the presence of organisms such as:

6307-3     Adenovirus rRNA [Presence] in Tissue by DNA probe  
 47396-7    *Babesia microti* DNA [Presence] in unspecified specimen by Probe and target amplification method  
 5002-1     Epstein Barr virus DNA [Presence] in Blood by Probe and target amplification method

are relatively easy to implement, e.g.:

| Table 1: SNOMED Coding Results for Qualitative IVDs |                                       |             |  |
|---|---------------------------------------|-------------|--|
| Assay/Device Result                                 | Interpretation from Labeling          | SNOMED Code | Comments   |
| <b>Detected</b>                                     | Detected, Positive, Present, etc.     | 260373001   | A valid test result indicates the presence of the analyte.   |
| <b>Not Detected</b>                                 | Not detected, Negative, Absent, etc.  | 260415000   | A valid test result indicates the absence of the analyte   |
| <b>Inconclusive</b>                                 | Inconclusive, indeterminate           | 419984006   | A valid result that cannot be used to draw a valid conclusion.                                     |
| <b>Test not completed</b>                           | Invalid test, Incomplete, Error, etc. | 373121007   | Test initiated but not completed due to device or control failure for an acceptable specimen type. |

Similarly, LOINC has > 200 antibody tests, e.g.,

170           22078-0   *Acanthamoeba sp* Ab [Presence] in cerebral spinal fluid  
171           12890-0   *Borrelia burgdorferi* 45kD Ab [Presence] in Serum by Immunoblot (IB)  
172           56131-6   Chikungunya virus IgM Ab [Presence] in Serum or Plasma by  
173                   Immunofluorescence

174   More sophisticated cases are when multiple analytes/results are possible. For example:

175       a.   A single test may report whether any one of 2 or more analytes is present but does not  
176           distinguish these (e.g., influenza A and/or influenza B). This is straightforward to report  
177           as there are only two possible responses i.e.,

- 178               a)   Positive for either A and/or B
- 179               b)   Negative for A and B

180       b.   A variant of this same test can detect which of two analytes is present in two ways and  
181           has two options for reporting:

182           1.   Use one variable to report all combinations of findings, i.e., one test name with a  
183               set of complex possible answers, e.g.:

- 184               a)   Negative for Influenza A and Influenza B
- 185               b)   Positive for Influenza A
- 186               c)   Positive for Influenza B
- 187               d)   Indeterminate<sup>15</sup>
- 188               e)   Positive for Influenza A and Influenza B

189           2.   Report the result for each detectable organism as a separate variables, each of  
190               which has a positive/negative result, e.g.:

- 191               a)   Influenza A
  - 192                   i.   Positive
  - 193                   ii.   Negative
  - 194                   iii.   Indeterminate
- 195               b)   Influenza B
  - 196                   i.   Positive
  - 197                   ii.   Negative
  - 198                   iii.   Indeterminate

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<sup>15</sup> This could be further expanded, e.g., Indeterminate for A and Positive for B, etc.



This latter example would likely represent the setting of a defined multiplex, e.g., currently marketed multiplexes (e.g., PCR devices), although these may have dozens of individual analytes.

3. Open ended results, (e.g., Blood culture, MALDI-TOF or genetic tests looking for a large set of mutations). These are most commonly reported in the following pattern:

- a) Analytes detected: Item A, Item C; Item F
- b) Analytes tested for e.g., Item A, item B, Item C, ... Item Z (indicates the analytes that could have been found if they were there)

Although the simplified example of Tables 1 is representative of only the most straightforward circumstance for illustration, it is intended to capture the concept of defining 'consensus' response sets that are applicable across large numbers of similar devices, and can be associated with specific IVDs by manufacturers/distributors. Recommended SNOMED values sets for various *in vitro* tests have been developed and published by different groups, e.g., coding for Influenza assays<sup>16</sup>, but a specific SNOMED response set, associated with a specific device as a component of device labeling (or otherwise associated with the device by the manufacturer) that is centrally maintained, updated, and accessible has been lacking.

Similar to the previous discussion, it has been proposed that FDA, CDC, and/or NLM can significantly assist Regenstrief in harmonizing the standardized result coding for answer lists that could be re-used widely to foster semantic interoperability. The analogous concept is creating interoperable response sets uniquely associated with a qualitative device as a LOINC-SNOMED response set or as a LOINC/SNOMED/UDI (Unique Device Identifier) tuple, etc., that could similarly be defined during device development and referred to in device labeling. The interoperable response set would be a subset of the broader device response set, i.e., coded

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<sup>16</sup> <http://www.cdc.gov/flu/professionals/diagnosis/rtpcr-test-kits.htm>

responses unique to a device that may not need to be reportable outside of the immediate use of the device and that may not require standardized coding.

At present, LOINC often includes example response sets as part of the definition of all LOINC terms with categorical answers. These usually represent the strings provided by the submitter verbatim--especially if the submitter is the IVD manufacturer/developer. There would be clear advantages to having device response sets that could be re-used across a class of tests (e.g., qualitative antibody tests) and having these represented as SNOMED codes, but such an effort poses greater challenges than the assignment of LOINC codes alone, particularly for existing devices. Mapping existing device descriptions to an interoperable set may require careful interpretation of the existing labeling, to avoid changes that will confuse care providers, and attention to any small differences that are important. However we believe that if this plan is implemented, for many categories of tests it would be possible to reach consensus for response sets along the lines illustrated by the examples above. In some cases the solution will require alternative coding options such that the literal string currently used could still be reported but a standard SNOMED code for the general meaning would also be included.

Given these considerations, we anticipate the SNOMED panelists addressing the following general questions:

- Please provide feedback on mechanisms to facilitate the assignment of LOINC-SNOMED code response sets as means to ensure consistent implementation across new IVDs. Address the potential benefits and challenges of such an approach, including the technical challenges of mapping LOINC to SNOMED response sets for qualitative *in vitro* diagnostic devices.
- Currently, one mechanism for obtaining code sets is for IVD manufacturers/developers submit their test to Regenstrief and Regenstrief creates answer lists which contain answers that correspond exactly to the answers they propose and/or are asserted in their package insert, subject to clarification from the LOINC specialists at Regenstrief. How can SNOMED coding be best reconciled with IVD manufacturer specific wording so

that reporting and interoperability can both be achieved; of note, there are places for both in the LOINC database and both could be sent in existing and planned HL7 messages.

- Which group/parties should lead in providing guidance to industry and the maintenance of new code sets. Are there possible means that FDA, CDC, NLM, or ONC could support and facilitate laboratory adoption of consistent SNOMED coding
- Please discuss current efforts and mechanisms that could facilitate manufacturer adoption of SNOMED coding to be associated with *in vitro* diagnostic devices.

#### **D. UCUM (Unified Code for Units of Measure)**

The purpose of UCUM is “is to facilitate unambiguous electronic communication of quantities together with their units.”<sup>17</sup> Similar to LOINC and SNOMED above, UCUM has been proposed as an unambiguous mechanism for interoperable reporting, specifically for describing quantitative results. It is required by HL7, DICOM and IEEE standards and in some federal standards for the reporting of measurements; ISO 11240 also makes UCUM a normative requirement for units of measure (UoM) as part of the ISO/ICH/IDMP effort.<sup>18</sup> LOINC already includes one (or more) example UCUM UoM representation for almost every laboratory and non-laboratory LOINC term in the database that identifies a quantitative measurement. These example UCUM units usually derived from the submitters units of measure for that LOINC term.

**Given these considerations, we anticipate UCUM panelists addressing the following general questions:**

- What are the benefits from and challenges to adopting UCUM for quantitative results with specific IVDs?
- Please describe additional mechanisms, if any, beyond LOINC assigning UCUM codes based on the submission units - coding necessary to identify appropriate UCUM coding.

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<sup>17</sup> <http://unitsofmeasure.org/trac/>

<sup>18</sup> International Organization for Standardization (ISO). ISO 11240:2012 - Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of units of measurement [Internet]. 2012 [cited 2015 Aug 17]; Available from: [http://www.iso.org/iso/iso\\_catalogue/catalogue\\_tc/catalogue\\_detail.htm?csnumber=55033](http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=55033)

- How can industry best work with federal entities to contribute to the adoption of UCUM?

#### E. UDI (Unique Device Identification)

UDI is an FDA-established system that "when fully implemented, the label of most devices will include a unique device identifier (UDI) in human- and machine-readable form."<sup>19</sup> Unique Device Identifiers are assigned by the manufacturer/sponsor through an FDA-accredited issuing agency such as GS1, HIBCC, or ICCBBA. FDA supports and maintains the Global Unique Device Identification Database (GUDID) that includes a device identifier lookup key for each model/version of the device and core device attributes associated with the device identifier. The National Library of Medicine provides public access to the GUDID via the AccessGUDID website.<sup>20</sup> An explicit goal of the UDI system is "... providing a standard and clear way to document device use in electronic health records, clinical information systems, claim data sources and registries..."<sup>21</sup>

The mapping from a UDI to an *individual in vitro* diagnostic test may be many to one (e.g., a large chemistry analyzer may perform > 100 individual assays), and when different specimen types are considered, a single UDI could potentially map to hundreds of LOINC codes. The UDI process and description permits granularity through the use of a 'virtual UDI' that would be able to distinguish subcomponents of devices that would be associated with many LOINC codes. Implementation of virtual UDIs, however, may be burdensome to manufacturers and require maintenance to consistently map to specific LOINC codes. (See the SMOMED example earlier which could reflect a single multiplex IVD device, and, accordingly, mapping of a single UDI to multiple LOINC codes.)

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<sup>19</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/>

<sup>20</sup> <https://accessgudid.nlm.nih.gov/>

<sup>21</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/BenefitsofaUDIsystem/default.htm99>

**F. Moving Forward:**

The Moving Forward panel at the workshop will focus on addressing the issues from the earlier discussions from the perspective of the proposed LOINC-SNOMED/UCUM/UDI system as a whole, including (but not limited to) the following questions:

- What is your opinion of the relative difficulty, and benefits of the effort needed to pursue each of three proposals: LOINC to identify individual tests, UCUM units of measure for quantitative tests, and SNOMED CT response sets for tests with categorical responses?
- What are the areas where different federal agencies can effectively interact with IVD manufacturers/distributors to optimize semantic interoperability? Are there mechanisms that could potentially integrate with current processes?
- What are the best ways to establish cooperative efforts or pilot projects to advance LOINC, SNOMED, and UCUM coding of IVDs?
- What are the approaches that should be considered/explored (or adopted) to disseminate coding information, e.g., centrally maintained versus distributed mechanisms? How would this information be maintained and validated?
- What is the role for UDI coding in the semantic interoperability of laboratory results, and how can this potential be best realized?
- What areas need to be addressed next to promote semantic interoperability and how should they be prioritized?

In summary, the focus of the Workshop will be discussion of possible mechanisms for predefining the association of *in vitro* diagnostic devices with LOINC codes and associated response sets, and how the sponsors of the workshop can contribute to this process. The organizers believe that possible benefits of unambiguous device-associated coding would be significant to all stakeholders and include the following: manufacturers would see more seamless adoption of devices in an increasingly interoperable medical environment; laboratories would lose the burden assigning codes and ensure meaningful use communication with other laboratories; public health researchers would gain enhanced

326 tools to identify early outbreaks and to track public health emergencies; and perhaps most  
327 importantly, interoperable coding would substantially aid in medical decision support and  
328 individual patient outcomes.

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